Off-Label Prescribing of Psychotropic Medication, 2005–2013: An Examination of Potential Influences

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Objective: This study examined rates of psychotropic prescriptions for various on- and off-label uses in 2005 and 2013 in the context of changes in labeled indications.

Methods: The National Disease and Therapeutic Index, a survey of nationally representative office-based physicians that identifies the diagnosis attached to each prescription, was used to capture the number of psychiatric medications prescribed for a particular diagnosis in 2005 (N=4,120) and 2013 (N=4,140). Labeled indications for each year were abstracted, and the association of prescribing patterns and changes in labeled indications was evaluated.

Results: Expanded labeling was associated with increased use of antidepressants for anxiety (an increase of 3.4 percentage points); antipsychotics for depression (8.3), bipolar disorder (3.4), and tic disorders, autism, and related disorders (1.5); and anxiolytics for anxiety disorders (5.5). Use of antidepressants for depression decreased, by 5.6 percentage points, as did use of antipsychotics (4.6) and anxiolytics (.7) for dementia-related disorders and of antipsychotics for attention-deficit and related disorders (2.7), likely reflecting black box warnings and evidence of side effects. Off-label use of antidepressants for attention deficit and related disorders and anxiolytics for bipolar disorders increased by 1.1 and 1.3 percentage points, respectively.

Conclusions: FDA labeling plays an important but imperfect role in influencing how providers select medications. Prescribing increases for medications with new indications. Conversely, black box warnings of potentially dangerous side effects result in decreased prescribing. However, labeled indications often lag the science, and prescribing patterns should be tracked to inform the need for more education, research, and labeling changes.

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Psychotropic medications are among the most widely prescribed drugs in the United States (1). They are prescribed for uses approved by the U.S. Food and Drug Administration (FDA) (on-label use) and for the treatment of diseases or populations for which FDA approval has not been received (off-label use). Off-label prescribing often occurs if there is no effective alternative for a particular patient population, such as a pediatric population; when a patient has not responded to other treatments; or when a patient's pathologic or physiologic features are similar to those approved for on-label use (2).

By law, manufacturers cannot promote off-label uses; however, scientific evidence may support these uses as an effective medical practice. The FDA does not directly regulate the practice of medicine or limit off-label prescribing. New indications may be added to a drug's label through a supplemental new drug application if the pharmaceutical manufacturer decides that the process justifies the cost (3). Obtaining a labeled indication requires a pharmaceutical manufacturer to invest time and money to gather the data and undergo the FDA submission process. This investment may not make financial sense, particularly if the medication has become generic (3). This may mean that there is a gap between what is known about the effectiveness of a medication and what is reflected in the label.

Investigating how medications are prescribed off label can help us understand the circumstances under which there may be a disincentive to obtain a change in a labeled indication, even when it seems necessary. It also may indicate situations in which more physician education is needed, such as when a particular off-label use has been shown to be harmful or ineffective but the medication is still being prescribed. Finally, examining off-label use can identify opportunities for more rigorous research to confirm perceived effectiveness in clinical practice.

The number of data sources with which one can identify off-label use is limited. Insurance claims databases have become a vital source of information on prescribing patterns; however, prescription drug claims do not include an associated diagnosis code. Moreover, psychiatric diagnoses often are excluded from medical insurance claims to avoid stigma, because they are secondary diagnoses, because of concerns about reimbursement, or for other reasons (4,5).

The National Disease and Therapeutic Index (NDTI) (6,7) is one of the few data sources that collects information on the drugs prescribed to patients and the diagnoses for which they were prescribed. We analyzed NDTI data from 2005 and 2013 to determine on- and off-label prescribing patterns and how they have changed over time.

METHODS

We used 2005 and 2013 data from the NDTI to analyze prescriber behavior (6,7). The NDTI obtains diagnostic and treatment data from an ongoing survey conducted by using a two-stage stratified cluster, which is randomly drawn. The survey, conducted by IMS Health, is completed by a panel of 4,140 nationally representative, office-based physicians (N=4,120 in 2005; N=4,140 in 2013). The NDTI panel draws from American Medical Association and America Osteopathic Association listings of physicians practicing in the continental United States. The panel is stratified by region and includes multiple specialties, for example, family and general practitioners and psychiatrists. The NDTI is similar to the National Ambulatory Medical Care Survey (NAMCS), sponsored by the Centers for Disease Control and Prevention, but it has more participants and specifically asks physicians about the condition for which they prescribed a particular medication. Physicians report data quarterly for all patient contacts during two consecutive workdays. Data are collected on approximately 2,760 workdays every month and 8,280 workdays every quarter. The survey uses a confidential logbook in which respondents record information for each drug recommended or issued to patients and the related diagnosis. A patient encounter may generate multiple diagnoses; however, the log provides a direct correspondence between each diagnosis and recommended medication. These recommendations, called "mentions" by the NDTI, may be equal to or greater than actual outpatient prescribing because patients may not fill all prescriptions and because physicians may link a single mention to multiple diagnoses, for example, by prescribing an antidepressant for both depression and anxiety. Results are projected to the national population of office-based physicians (8). Additional information on the sample methodology is provided by Mark (9).

We grouped mentions into three categories of medication (antidepressants, antipsychotics, and anxiolytics) by using the 2014 Uniform System of Classification (10). Sedative hypnotics were excluded from the anxiolytics studied. We used *ICD-9-CM* (11) codes to categorize diagnoses as psychiatric (codes 290–314) or nonpsychiatric. Diagnoses were grouped with Agency for Healthcare Research and Quality Clinical Classifications Software, a categorization that combines related *ICD-9-CM* codes (12). We grouped diagnoses into general categories, for example, anxiety disorders and depression. We also listed the ten most commonly identified nonpsychiatric uses for each type of medication in 2013, supplemented with others that were ranked as most common in the 2005 data to allow complete comparison across years, and grouped all others into an "other" category. The percentage of mentions of each drug category per diagnosis for 2005 and 2013 and changes in percentage points between 2005 and 2013 were calculated. Standard errors were calculated by using tables of relative standard errors that accounted for the complex NDTI sampling design, and two-sample z-tests were applied, allowing calculation of p values.

Next, we examined changes in labeling between 2005 and 2013 for drugs in each class by using current and historical labeling data available at Drugs@FDA (13), DailyMed (14), or 2003 and 2005 editions of the *Physicians' Desk Reference* (15,16). We examined the extent to which changes in mentions between 2005 and 2013 coincided or conflicted with labeled indications during that time.

Last, a literature scan examined whether changes in the scientific evidence or in major treatment guidelines between 2003 and 2013—apart from labeling changes—might have influenced prescriber behavior.

RESULTS

Antidepressants

Table 1 describes labeled indications for antidepressants in 2005 and indications that were added between 2005 and 2013. In 2005, most antidepressants were labeled only for depression. A few were labeled for anxiety disorders, such as obsessive-compulsive disorder and panic disorder, and some were labeled for nonpsychiatric conditions. By 2013, additional indications for anxiety disorders had been added to several selective serotonin reuptake inhibitors (SSRIs) (paroxetine mesylate; fluvoxamine mal and mal ER; paroxetine CR, HLC, and HCL ER; and fluoxetine HCL) and a serotonin–norepinephrine reuptake inhibitor (SNRI) (duloxetine HCL). Indications were added for two tricyclic and tetracyclic antidepressants—manic-depressive illness, depressed type, for maprotiline HCL and insomnia for doxepin HCL. In addition, nonpsychiatric indications were added for a newer-generation antidepressant—severe hepatic impairment for bupropion hydrobromide; an SSRI—moderate to severe vasomotor symptoms associated with menopause for paroxetine mesylate; and an SNRI—diabetic peripheral neuropathic pain, fibromyalgia, and chronic musculoskeletal pain for duloxetine HCL.

Other pertinent labeling changes occurred shortly before 2005. In 2004, the FDA began requiring a black box warning reflecting increased evidence of risk of suicidality among adolescents (17); in 2007, the warning was extended for persons up to age 24 (18). FDA also issued a warning that antidepressant use may increase the risk of mania for certain individuals (19).

Consistent with additional labeling for anxiety and warnings related to suicidality, Table 2 shows a large increase of 3.4 percentage points in antidepressant mentions for anxiety disorders and a decline of 5.6 percentage points in mentions for depression ($p<.001$ for both). Off-label uses for certain diagnoses, such as attention-deficit, conduct, and disruptive behavior disorders, also increased, by 1.1 percentage points ($p<.001$).

TABLE 1. FDA-approved uses for antidepressants in 2005 and 2013[a]

Classification and drug[b]	2005[c]	2013
Tricyclics and tetracyclics		
Amoxapine	Depression	
Clomipramine HCL	OCD	
Amitriptyline HCL	Depression	
Maprotiline HCL	Depression and anxiety associated with depression	Dysthymic disorder and manic-depressive illness, depressed type
Desipramine HCL	Depression	
Nortriptyline HCL	Depression	
Mirtazapine	Major depressive disorder	
Doxepin HCL	Depression or anxiety (including associated with alcoholism or with organic disease), psychotic depressive disorders, short-term management of moderate pruritus in adults with atopic dermatitis or lichen simplex chronicus	Insomnia
Imipramine HCL, imipramine pamoate, trimipramine maleate	Depression and childhood enuresis	
Protriptyline HCL	Depression	
MAO inhibitors		
Selegiline	Major depressive disorder	
Isocarboxazid	Major depressive disorder	
Phenelzine sulfate	Depression	
Tranylcypromine sulfate	Major depressive episode without melancholia	
Newer-generation antidepressants		
Bupropion hydrobromide		Major depressive disorder, seasonal affective disorder, severe hepatic impairment
Bupropion HCL, bupropion HCL SR, bupropion HCL XL	Major depressive disorder, smoking cessation treatment	
Trazodone HCL	Major depressive disorder	
Nefazodone HCL	Depression	
SSRIs		
Paroxetine mesylate	Major depressive disorder, OCD, panic disorder	Generalized anxiety disorder, moderate to severe vasomotor symptoms associated with menopause
Citalopram HBR	Depression	
Escitalopram oxalate	Major depressive disorder, generalized anxiety disorder	
Fluvoxamine mal, fluvoxamine mal ER	OCD	Social anxiety disorder
Paroxetine CR, paroxetine HCL, paroxetine HCL ER	Major depressive disorder, panic disorder, premenstrual dysphoric disorder	OCD, social anxiety disorder, generalized anxiety disorder, PTSD
Fluoxetine HCL	Depression, OCD	Bulimia, panic disorder, premenstrual dysphoric disorder
Sertraline HCL	Major depressive disorder, OCD, panic disorder, PTSD, premenstrual dysphoric disorder, social anxiety disorder	
SNRIs		
Duloxetine HCL	Major depressive disorder	Diabetic peripheral neuropathic pain, generalized anxiety disorder, fibromyalgia, chronic musculoskeletal pain
Venlafaxine HCL, venlafaxine HCL ER	Major depressive disorder, generalized anxiety disorder, social anxiety disorder, panic disorder	
Levomilnacipran HCL	Not on the market	Major depressive disorder
Desvenlafaxine ER	Not on the market	Major depressive disorder
SSRI/5-HT partial agonists		
Vortioxetine hydrobromide	Not on the market	Major depressive disorder
Vilazodone hydrochloride	Not on the market	Major depressive disorder
Antidepressants in combination with other drugs		
Perphenazine and amitriptyline	Depression	
Amitriptyline and chlordiazepoxide	Depression	Moderate to severe depression associated with moderate to severe anxiety

[a] Most approved drug uses were obtained from Drugs@FDA (13). Abbreviations: 5HT, 5-hydroxytryptamine; CR, controlled release; ER, extended release; FDA, U.S. Food and Drug Administration; HCL, hydrochloride; MAO, monoamine oxidase; SNRIs, serotonin-norepinephrine reuptake inhibitors; SR, slow release; SSRIs, selective serotonin reuptake inhibitors; XL, extended release; OCD, obsessive-compulsive disorder; PTSD, posttraumatic stress disorder

[b] From the Uniform System of Classification Cross-Reference File, 2014 (10)

[c] Labeling information for some older drugs was obtained from DailyMed (14).

TABLE 2. National estimates of antidepressant mentions in 2005 and 2013, by patient diagnosis and FDA labeling for an approved use[a]

Diagnosis[c]	All mentions (%)		Change in mentions			Labeling[b]	
	2005	2013	Percentage points	SE	p	2005	2013
Psychiatric	92.7	92.0	−.7	.0780	<.001	—	—
Depressive disorders	56.4	50.8	−5.6	.5263	<.001	Yes	+
Bipolar disorders	7.6	7.5	−.1	.0240		No	+
Anxiety disorders	16.4	19.8	3.4	.5464	<.001	Yes	+
Attention-deficit, conduct, and disruptive behavior disorders	2.8	3.9	1.1	.2096	<.001	No	No
Schizophrenia and other psychotic disorders	2.6	2.3	−.3	.0824	<.001	No	No
Adjustment disorders	1.3	.9	−.4	.1099	<.001	No	No
Personality disorders	.7	.9	.2	1.1242	ns	No	No
Miscellaneous disorders	.9	.8	−.1	.0346	<.01	—	—
Delirium, dementia, and amnestic and other cognitive disorders	1.0	.8	−.2	.0693	<.01	No	No
Alcohol and other substance-related disorders	.3	.7	.4	1.0935	ns	No	No
Disorders usually diagnosed in infancy, childhood, or adolescence	.2	.6	.4	.3383	ns	No	No
Screening and history of mental health and substance abuse codes	.8	.4	−.4	.1099	<.001	No	No
Impulse control disorders not otherwise classified	.2	.2	.0	.0000	—	No	No
Developmental disorders	.0	.0	.0	.0000	—	No	No
Nonpsychiatric	7.3	8.0	.7	1.0832	ns	—	—
Other connective tissue disease	1.1	1.9	.8	.2623	ns	No	+
Headache, including migraine	1.1	1.3	.2	.0693	ns	No	No
Spondylosis, intervertebral disc disorders, and other back problems	.7	.7	.0	.0000	—	No	No
Other nervous system disorders	.8	.6	−.2	.0693	<.01	No	No
Diabetes mellitus with complications	.3	.4	.1	.0346	ns	No	+
Osteoarthritis	.0	.3	.3	.1039	ns	No	No
Menopausal disorders	.3	.2	−.1	.0346	<.01	No	+
Other female genital disorders	.8	.2	−.6	.1309	<.001	No	No
Other aftercare	.1	.2	.1	.0346	ns	No	No
Other gastrointestinal disorders	.1	.2	.1	.0346	ns	No	No
Other[d]	2.0	1.8	−.2	.0693	<.01	—	—
Other residual codes; unclassified	2.0	2.8	.8	.1745	<.01	—	—

[a] From the 2005 and 2013 National Disease and Therapeutic Index (6,7), a survey of nationally representative office-based physicians that captures each mention of a psychiatric medication and the diagnosis for which it is recommended. Diagnosis categories are based on the Agency for Healthcare Research and Quality's Clinical Classifications Software (CCS) (12). Medications are categorized according to Uniform System of Classification coding (10). Residual codes and unclassified diagnoses include codes or diagnoses that are unclassified according to the CCS.

[b] No, not labeled for that indication; yes, labeled for that indication; +, new or additional labels for that indication; —, labeling not addressed as a composite category

[c] All entries, some of which are not strictly diagnoses, are based on *ICD-9-CM* codes.

[d] The other category includes a large number of diagnoses with a small number of mentions. Data are reported for the top ten most common diagnoses in this category in 2013, supplemented by others frequently seen in the 2005 data.

Antipsychotics

Table 3 describes labeled indications for antipsychotics in 2005 and 2013. In 2005, most antipsychotics were labeled for bipolar disorders and psychotic disorders, including schizophrenia. Perphenazine and chlorpromazine HCL were labeled for nausea and vomiting, and carbamazepine was labeled for epilepsy and trigeminal neuralgia. Besides having indications for bipolar disorders and psychotic disorders, chlorpromazine HCL had several other indications, including presurgery apprehension, acute intermittent porphyria, tetanus, and intractable hiccups. Trifluoperazine HCL was labeled as a second-line treatment for nonpsychotic anxiety. Pimozide was labeled as a second-line treatment of Tourette's disorder.

Shortly before 2005, black box labels were placed on antipsychotic medications warning of an increased risk of death when prescribed to older adults with dementia (20). By 2013, labeling for several antipsychotics had been increased to include the treatment of specific aspects of psychotic disorders and bipolar disorders and various age groups. New medications for these disorders were also available. Indications had been added for treatment of depression (olanzapine/fluoxetine HCL and aripiprazole) and the depressive phase of bipolar disorder (quetiapine fumarate and loxapine). For certain antipsychotics, labeling was also added for treatment of tics associated with Tourette's disorder (haloperidol) and irritability associated with autistic disorder (risperidone and aripiprazole) and for short-term or second-line treatment for severe behavior problems or hyperactivity among children (haloperidol).

Consistent with additional labeling for depression, bipolar disorder, tics, and autism-related behaviors, Table 4 shows large increases between 2005 and 2013 in the number of antipsychotic mentions for depression, which increased by 8.3 percentage points, and for bipolar disorder, which increased by 3.4 percentage points ($p<.001$ for both). Antipsychotic mentions also increased, by 1.5 percentage points, for disorders usually diagnosed in infancy, childhood, or adolescence (which encompass autism and tic disorders) ($p<.05$). Mentions increased by 1.0 percentage point for schizophrenia and other psychotic disorders ($p<.001$) and by .7 percentage point for anxiety disorders ($p<.05$). The largest

decrease in antipsychotic mentions, 4.6 percentage points, was for delirium, dementia, and amnestic and other cognitive disorders, an off-label use that was the subject of a black box warning in 2005, followed by a decrease of 2.7 percentage points in mentions for attention-deficit, conduct, and other disruptive behavior disorders ($p<.001$ for both).

Anxiolytics

In 2005, anxiolytics were labeled for treatment of anxiety disorders and anxiety symptoms, alcohol withdrawal, sedation, and the prevention of preoperative anxiety. Some anxiolytics also had indications for allergic conditions, epilepsy, stiffness, and other conditions. By 2013, some anxiolytics had indications for generalized anxiety disorder, sedation, and epilepsy. The label for hydroxyzine added indications for nausea and vomiting, labor and other pain, reduction in narcotic use among pregnant and postpartum women, and psychomotor agitation. Anxiolytics were not approved at any point in the study period for treating dementia; labels for anxiolytics contained precautions about use among older adults, and benzodiazepines were expressly excluded from Medicare Part D coverage from 2006 through 2012 because of concerns about side effects (21,22). [A table listing labeled indications for anxiolytics in 2005 and 2013 is available as an online supplement to this article.]

Table 5 shows a large increase of 5.5 percentage points in the number of anxiolytic mentions for anxiety ($p<.001$). Off-label use of anxiolytics for bipolar disorders also increased, by 1.3 percentage points ($p<.05$). There was a decrease of .8 percentage point in on-label use for medical examination or evaluation ($p<.001$) and of .7 percentage point in off-label use for delirium, dementia, and amnestic and other cognitive disorders ($p<.01$); the latter decline was consistent with label warnings and Medicare reimbursement changes.

DISCUSSION

FDA labeling plays a major role in influencing how providers select medications to prescribe for specific conditions. The addition of new indications for a class of drugs or even the expansion of indications to more drugs in the same class provides an imprimatur for such prescribing and allows pharmaceutical manufacturers to advertise a product for new indications or populations. These data confirm that psychotropic prescribing responds to the addition of new labeled indications. The increased use of antidepressants for anxiety disorders and pain and of antipsychotics for depression, bipolar disorder, and disorders diagnosed in childhood is consistent with a rise in the number of labeling indications as well as with increased information regarding efficacy (23–29). As one example, the increase of 1.5 percentage points in antipsychotic mentions for disorders usually diagnosed in childhood reflects the addition of indications to address irritability associated with autistic disorder and additional indications for tics associated with Tourette's disorder, prompted by evidence that had accumulated supporting prescribing of antipsychotics for those uses (24–26,30). Antipsychotics were prescribed for these disorders in 2005, before the label changes, but such use increased by 2013, as additional labeling was attained. Antipsychotic use for schizophrenia and other psychotic disorders also increased but by the lesser amount of 1.0 percentage point, accompanying the addition of new medications in the market and new indications for new populations (children and adolescents).

These analyses also confirm that prescribers respond to black box warnings and associated evidence of side effects and risk associated with prescribing medications to particular populations, for particular conditions, or both. The percentage of antidepressant mentions for depression decreased by 5.6 percentage points between 2005 and 2013. This decline was likely associated with black box warnings of the risk of mania and the risk of suicide associated with use of antidepressants among young people. Similarly, use of both antipsychotics and anxiolytics for the treatment of dementia decreased, by 4.6 and .7 percentage points, respectively, reflecting black box warnings, scientific evidence of increased risk of falls and other morbidity among elderly persons (22,31), and policies limiting coverage, such as the exclusion of benzodiazepines from Medicare coverage (21,22,31–34). Our findings related to antipsychotics coincide with those of Driessen and others (33), who found that antipsychotics were increasingly unlikely to be dispensed between 2010 and 2012 for treatment of dementia among elderly Medicare beneficiaries. At no point in the study period were antipsychotics labeled as appropriate for the treatment of dementia-related disorders.

The causes of some changes in prescribing are less obvious. For instance, reasons for the decrease of 2.7 percentage points in antipsychotic mentions for attention-deficit, conduct, and disruptive behavior disorders are ambiguous. As of 2005, chlorpromazine HCL was labeled for severe behavioral problems among children, including short-term treatment of hyperactivity. After 2005, haloperidol also was labeled for this indication, albeit accompanied by distinct warnings that it be used only after other approaches have failed. Countering this labeling addition were published reports indicating a growing concern about increased use of antipsychotics for such disorders, especially involving prescribing by nonpsychiatrists (35,36) and overuse in lieu of other treatments (35–37). These concerns may have outweighed any increase in prescribing associated with the newly labeled indications. Notably, this decrease was accompanied by a nonsignificant increase of 1.4 percentage points in anxiolytic mentions for these disorders, perhaps evidence that one sedating medication had been substituted for another.

This study revealed examples of off-label prescribing that increased between 2005 and 2013 (for example, use of antidepressants for attention-deficit, conduct, and disruptive behavior disorders and use of anxiolytics for bipolar disorder) and examples in which use persisted, albeit at lower

TABLE 3. FDA-approved uses for antipsychotics in 2005 and 2013[a]

Classification and drug[b]	2005[c]	2013
Phenothiazine derivatives		
Thioridazine HCL	Schizophrenia, if there is insufficient response to other antipsychotic drugs	
Fluphenazine HCL and fluphenazine decanoate	Manifestations of psychotic disorders; management of patients requiring prolonged parenteral neuroleptic therapy, for example, individuals with chronic schizophrenia	
Trifluoperazine HCL	Schizophrenia and short-term treatment of generalized nonpsychotic anxiety (not as initial therapy)	
Chlorpromazine HCL	Schizophrenia, nausea and vomiting, restlessness and apprehension before surgery, acute intermittent porphyria, adjunct in the treatment of tetanus, bipolar mania, intractable hiccups, severe behavioral problems in children ages 1–12 years, short-term treatment of hyperactivity in children	
Perphenazine	Schizophrenia, management of manifestations of psychotic disorders, control of severe nausea and vomiting in adults	
Antipsychotics, combined	Medications are categorized according to Uniform System of Classification (USC) coding (10).	
Olanzapine/ fluoxetine HCL	Depressive episodes associated with bipolar disorder	Treatment-resistant depression
Antipsychotics, other		
Aripiprazole	Schizophrenia, acute manic and mixed episodes associated with bipolar disorder	Treatment of schizophrenia among adults and adolescents ages 13–17 years; adjunctive treatment of major depressive disorder among adults; treatment of adults with agitation associated with schizophrenia or bipolar I disorder, manic or mixed; treatment of acute manic or mixed episodes associated with bipolar I disorder among pediatric patients ages 10–17 years; treatment of manic or mixed episodes associated with bipolar I disorder as monotherapy or adjunctive to lithium or valproate amomg adults and pediatric patients ages 10–17 years; maintenance treatment of bipolar I disorder; treatment of irritability associated with autistic disorder among pediatric patients ages 6–17 years
Clozapine	Management of severely ill schizophrenic patients who do not respond adequately to standard drug treatment for schizophrenia; reducing the risk of recurrent suicidal behavior among patients with schizophrenia or schizoaffective disorder who are judged to be at chronic risk of reexperiencing suicidal behavior	
Carbamazepine	Acute manic and mixed episodes associated with bipolar I disorder; epilepsy—partial, generalized and mixed types; trigeminal neuralgia	
Iloperidone	Not on the market	Acute treatment of schizophrenia among adults
Clozapine ODT	Management of severely ill patients with schizophrenia who do not respond adequately to standard drug treatment for schizophrenia	Reduction of the risk of recurrent suicidal behavior among patients with schizophrenia or schizoaffective disorder who are judged to be at chronic risk of reexperiencing suicidal behavior
Ziprasidone HCL or ziprasidone mesylate	Schizophrenia, bipolar mania, intramuscular administration for acute agitation in schizophrenia	Acute treatment as monotherapy of manic or mixed episodes associated with bipolar I disorder, maintenance treatment of bipolar I disorder as an adjunct to lithium or valproate

continued

TABLE 3, *continued*

Classification and drug[b]	2005[c]	2013
Haloperidol or haloperidol deconate or haloperidol lactate	Schizophrenia	Severe behavior problems of combative, explosive hyperexcitability (which cannot be accounted for by immediate provocation) among children and short-term treatment of hyperactive children who show excessive motor activity with accompanying conduct disorders consisting of some or all of the following: impulsivity, difficulty sustaining attention, aggressivity, mood lability, and poor frustration tolerance; haloperidol should be reserved for these two groups of children only after there has been no response to psychotherapy or medications other than antipsychotics; tics associated with Tourette's disorder
Paliperidone or paliperidone palmitate	Not on the market	Schizophrenia, schizoaffective disorder as monotherapy and as an adjunct to mood stabilizers or antidepressants, schizophrenia among adolescents ages 12–17 years
Lurasidone HCL	Not on the market	Schizophrenia
Loxapine HCL or loxapine succinate	Schizophrenia	As an inhalation powder; for use in enrolled health care facilities only for acute treatment of schizophrenia or bipolar I disorder among adults; bipolar disorder, depressed phase
Molindone HCL	Schizophrenia	
Thiothixene or thiothixene HCL	Schizophrenia	
Pimozide	Tics associated with Tourette's disorder if patient failed to respond to standard treatment	
Risperidone	Schizophrenia, acute manic or mixed episodes associated with bipolar I disorder as monotherapy or as adjunctive therapy with lithium or valproate	Irritability associated with autistic disorder, for example, symptoms of aggression toward others, deliberate self-injuriousness, temper tantrums, and quickly changing moods, among children and adolescents ages 5–16 years; schizophrenia among adolescents ages 13–17 years; treatment of acute episodes alone for children ages 5–16 years; monotherapy or as adjunctive therapy to lithium or valproate for the maintenance treatment of bipolar I disorder
Asenapine maleate	Not on the market	Acute treatment of schizophrenia among adults; as monotherapy or adjunctive therapy, acute treatment of manic or mixed episodes associated with bipolar I disorder among adults
Quetiapine fumarate	Bipolar mania, schizophrenia	Depressive episodes associated with bipolar disorder
Olanzapine or olanzapine ODT or olanzapine pamoate	Schizophrenia, bipolar disorder	Agitation associated with schizophrenia and bipolar I mania; acute treatment of manic or mixed episodes with bipolar I disorder and maintenance treatment of bipolar I disorder, with special considerations in treating pediatric schizophrenia and bipolar mania

[a] Most approved drug uses were obtained from Drugs@FDA (13). Abbreviations: FDA, U.S. Food and Drug Administration; HCL, hydrochloride; ODT, orally disintegrating tablet

[b] From the Uniform System of Classification Cross-Reference File, 2014 (10)

[c] Labeling information for some older drugs was obtained from DailyMed (14) and the *Physicians' Desk Reference* (15,16).

rates, despite black box warnings (use of antipsychotics and anxiolytics for dementia). It is important to ask why off-label uses that are contraindicated persist. Tracking on- and off-label prescribing is important to inform the need for education, research, and labeling changes.

One important implication of this work is the need to evaluate barriers and incentives that affect whether pharmaceutical manufacturers apply for labeling changes related to new indications. Companies can file supplemental new drug applications, following earlier approval, to add indications. Recent reviews have found, however, that new drug applications are not commonly used (38). In some instances, labeling for new indications may be appropriate but disincentivized.

TABLE 4. National estimates of antipsychotic mentions in 2005 and 2013, by patient diagnosis and FDA labeling for an approved use[a]

Diagnosis[c]	All mentions (%)		Change in mentions			Labeling[b]	
	2005	2013	Percentage points	SE	p	2005	2013
Psychiatric	98.9	99.0		.0128	<.001	—	—
Depressive disorders	5.3	13.6	8.3	1.5817	<.001	No	+
Bipolar disorders	26.4	29.8	3.4	.5464	<.001	Yes	+
Schizophrenia and other psychotic disorders	34.5	35.5	1.0	.1607	<.001	Yes	+
Anxiety disorders	5.5	6.2	.7	.1680	<.05	Yes	=
Disorders usually diagnosed in infancy, childhood, or adolescence	2.3	3.8	1.5	.3601	<.05	No	+
Attention-deficit, conduct, and disruptive behavior disorders	5.7	3.0	−2.7	.5889	<.001	Yes	+
Delirium, dementia, and amnestic and other cognitive disorders	7.4	2.8	−4.6	.8325	<.001	No	No
Personality disorders	1.5	1.3	.2	.0693	<.01	No	No
Developmental disorders	.5	.7	.2	.0693	ns	No	No
Impulse control disorders not otherwise classified	1.2	.6	−.6	.2078	<.01	Yes	+
Alcohol and other substance-related disorders	.7	.5	−.2	.0693	<.01	No	No
Adjustment disorders	.2	.2	.0	.0000	—	No	No
Miscellaneous disorders	.4	.2	−.2	.0693	<.01	—	—
Nonpsychiatric	1.1	1.1	.0	.0000	—	—	—
Coma, stupor, and brain damage	.0	.3	.3	.1039	ns	No	No
Headache, including migraine	.0	.2	.2	.0693	ns	No	No
Epilepsy, convulsions	.0	.1	.1	.0346	ns	No	No
Spondylosis, intervertebral disc disorders, and other back problems	.0	.1	.1	.0346	ns	No	No
Other connective tissue disease	.0	.1	.1	.0346	ns	No	No
Parkinson's disease	.0	.1	.1	.0346	ns	No	No
Other aftercare	.1	.1	.0	.0000	—	No	No
Abdominal pain	.0	.1	.1	.0346	ns	No	No
Other hereditary and degenerative nervous system conditions	.2	.1	−.1	.0346	<.01	No	No
Paralysis	.0	.0	.0	.0000	—	No	No
Intracranial injury	.2	.0	−.2	.0693	<.01	No	No
Diabetes mellitus with complications	.1	.0	−.1	.0346	<.01	No	No
Nausea and vomiting	.1	.0	−.1	.0346	<.01	Yes	+
Other nutritional, endocrine, and metabolic disorders	.1	.0	−.1	.0346	<.01	Yes	=
Other[d]	.2	.1	−.1	.0346	<.01	—	—
Other residual codes; unclassified	1.8	1.0	−.8	.2909	<.01	—	—

[a] From the 2005 and 2013 National Disease and Therapeutic Index (6,7), a survey of nationally representative office-based physicians that captures each mention of a psychiatric medication and the diagnosis for which it is recommended. Diagnosis categories are based on the Agency for Healthcare Research and Quality's Clinical Classifications Software (CCS) (12). Medications are categorized according to Uniform System of Classification coding (10). Residual codes and unclassified diagnoses include codes or diagnoses that are unclassified according to the CCS.

[b] No, not labeled for that indication; yes, labeled for that indication; +, new or additional labels for that indication; —, labeling not addressed as a composite category.

[c] All entries, some of which are not strictly diagnoses, are based on *ICD-9-CM* codes.

[d] The other category includes a large number of diagnoses with a small number of mentions. Data are reported for the top ten most common diagnoses in this category in 2013, supplemented by others frequently seen in the 2005 data.

Another important consideration is the nature of the current psychiatric diagnostic schema that serves as the basis for labeled indications. These systems (*ICD* and *DSM*) are based on psychiatric symptoms, which often are heterogeneous across diagnoses. As the former director of the National Institute of Mental Health (NIMH) pointed out, "The symptom of anxiety, for instance, can represent an endocrine disorder, a psychotic process, a drug response, or one of the currently recognized anxiety disorders." (39) NIMH is conducting the first steps toward developing a new diagnostic approach that integrates information besides symptoms, but this effort is still in its infancy.

This study had potential limitations. It used mentions of recommended medication as a proxy for actual treatment, which may overstate dispensed medications because patients may not obtain a recommended prescription and may understate dispensed medications because they exclude refills and inpatient prescribing. Therefore, results for certain diagnostic categories or classes of drugs may differ from results that are based on dispensed medications from all settings, such as hospitals, or on data on prescriptions filled. Also, although the NDTI is the only data set that links a medication to a diagnosis, it is possible that participation as a panel member may influence the types of medications mentioned. Although the sample was selected and weighted to be nationally representative, we cannot be certain that the participating physicians were not more cautious in off-label prescribing. We also do not know the response rate for the physicians because that is proprietary information, but we know that the response rate for the NDTI is lower than for government surveys (40). Similarly, the inability to incorporate patient information limited the ability to link changes in drug mentions with age-related changes in labeling. Also, because we did not separate drug mentions by physician type, we cannot report whether the results differed between psychiatrists and other physicians. Last, additional research that studies mentions by specific medication rather than by drug class would allow greater granularity in analyzing off-label prescribing by connecting each drug mention to a particular label.

Despite its limitations, the NDTI is the only data set that links a medication to a diagnosis. The NDTI, claims data, and data from surveys such as the NAMCS all include diagnoses and medication information, but they do not report the information in the same way. In claims or NAMCS data, multiple diagnoses may be listed, and it is impossible to determine the diagnosis for which a medication was prescribed. Similarly, if no psychiatric diagnosis is identified, it is impossible to ascertain the prescriber's intention. Although the NAMCS could provide similar information, it currently does not. The NDTI, on the other hand, preserves the necessary linkage between medication and diagnosis and provides unique insight into office-based physicians' perceptions of appropriate pharmacologic treatment. Similarly, although claims data capture only prescriptions reimbursed by the pertinent payer, NDTI data include information about all prescriptions, regardless of insurer, including prescriptions paid for out of pocket. Rather, the data capture the prescription the provider would "write" if reimbursement and patient preference were not considerations. In that sense, they capture the provider's vision of what should be prescribed rather than what can be prescribed.

TABLE 5. National estimates of anxiolytic mentions in 2005 and 2013, by patient diagnosis and FDA labeling for an approved use[a]

Diagnosis[c]	All mentions (%)		Change in mentions			Labeling[b]	
	2005	2013	Percentage points	SE	p	2005	2013
Psychiatric	67.7	76.3	8.3	1.0587	<.001	—	—
Anxiety disorders	39.6	45.1	5.5	.8839	<.001	Yes	+
Depressive disorders	14.4	14.4	.0	.0000	—	No	No
Bipolar disorders	3.9	5.2	1.3	.3121	<.05	No	No
Alcohol and other substance-related disorders	1.9	2.8	.9	.2473	ns	Yes	+
Schizophrenia and other psychotic disorders	2.1	2.5	.4	.1385	ns	No	No
Attention-deficit, conduct, and disruptive behavior disorders	.8	2.2	1.4	.3847	ns	No	No
Adjustment disorders	1.5	1.3	−.2	.0693	<.01	No	No
Personality disorders	.8	.9	.1	.0346	ns	No	No
Delirium, dementia, and amnestic and other cognitive disorders	1.2	.5	−.7	.2424	<.01	No	No
Miscellaneous mental disorders	.3	.3	.0	.0000	—	—	—
Disorders usually diagnosed in infancy, childhood, or adolescence	.1	.3	.2	.0693	ns	No	No
Developmental disorders	.1	.2	.1	.0346	ns	No	No
Impulse control disorders not otherwise classified	.3	.1	−.2	.0693	<.01	No	No
Screening and history of mental health and substance abuse codes	.1	.0	−.1	.0346	<.01	No	No
Nonpsychiatric	32.3	24.0	−8.3	1.3339	<.001	—	—
Medical examination or evaluation	6.0	4.2	−1.8	.4321	<.001	Yes	+
Allergic reactions	4.1	3.5	−.6	.2078	<.01	Yes	=
Spondylosis, intervertebral disc disorders, and other back problems	2.5	1.9	−.6***	.2078	<.01	No	No
Epilepsy, convulsions	1.2	1.2	.0	.0000	—	Yes	+
Other connective tissue disease	.8	1.0	.2	.0693	ns	Yes	=
Conditions associated with dizziness or vertigo	.5	.9	.4	.1385	ns	No	No
Other inflammatory condition of skin	.9	.8	−.1	.0346	<.01	No	No
Other skin disorders	.8	.8	.0	.0000	—	No	No
Other aftercare	1.3	.7	−.6	.2078	<.01	No	No
Sprains and strains	.9	.7	−.2	.0693	<.01	No	No
Other[d]	10.2	8.0	−2.2	.5281	<.001	—	—
Other residual codes; unclassified	2.8	3.0	.2	.0693	ns	—	—

[a] From the 2005 and 2013 National Disease and Therapeutic Index (6,7), a survey of nationally representative office-based physicians that captures each mention of a psychiatric medication and the diagnosis for which it is recommended. Diagnosis categories are based on the Agency for Healthcare Research and Quality's Clinical Classifications Software (CCS) (12). Medications are categorized according to Uniform System of Classification coding (10). Residual codes and unclassified diagnoses include codes or diagnoses that are unclassified according to the CCS.

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CONCLUSIONS

These findings highlight that labels are an important but imperfect guide for physicians to make prescribing decisions. This may be particularly true in psychiatry, given that the diagnostic schema that forms the basis for labels is highly imprecise. Tracking prescribing for labeled and off-label conditions is a useful tool for illuminating whether new labeled indications may be appropriate, whether research on new indications and contraindicated indications is needed, and whether physicians may benefit from additional education about the application of particular medications for particular clinical scenarios.

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